Acylanthranils. 7. Influence of the End Group on Selectivity in the Reaction of ω-Substituted Linear Aliphatic Amines with Acetylanthranil[1]

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The reaction of acetylanthranil (1) with the amines $H_2N(CH_2)_4(CH_2)_{n-4}Z$ (**2a, 2b, 3c**) follows pathway B when Z is H (**2a**), but it follows pathway A when Z is a polar group such as OH (**2b**) or CO_2H (**2c**). This remote control on reaction selectivity at the other extremity is attributed to steric hindrance to reaction with 1 imparted by the $H_2N(CH_2)_4$– segment, which is held in the form of a six-membered Newman coil by the force of intramolecular association of the van der Waals type when Z is H, but which is overcome by intermolecular hydrogen bonding when Z is a OH or CO_2H. The reaction follows pathway B, however, when the terminal group is esterified.

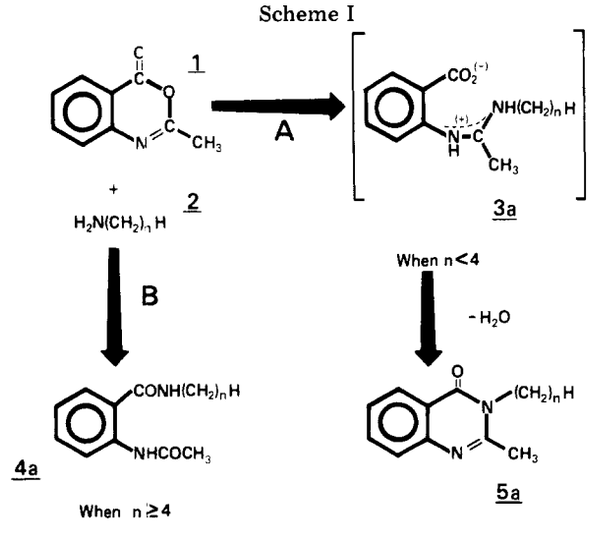
It was observed[2,3] that the pK_a value for the amines in the homologous series $H_2N(CH_2)_nH$ (**2a**) does not increase with n to an asymptotic limit as expected but rather peaks at $n = 2$ and then falls to a lower value, which remains relatively constant over the range from $n = 4$ to 22. This observation led to the speculation[3] that only the third and/or fourth methylene groups are responsible for this deviation from ideality, since increasing the chain further does not increase the deviation.

Hard evidence in support of this speculation was noted in the product distributions obtained in the reaction of acetylanthranil (1) with the amines **2a** neat or in an organic solvent.[3] Those amines with $n < 3$ followed pathway A exclusively to give the corresponding *N*-(2-carboxyphenyl)acetamidine salt **3** or its cyclodehydration product **5**; whereas those amines with $n > 3$ followed pathway B exclusively to give the corresponding *o*-acetamidobenzamide **4** as shown in Scheme I. Although reaction with *n*-propylamine (**2a**; $n = 3$) was dominated by pathway A, reaction via the alternate pathway was somewhat competitive. The exact selectivity ratio, however, depended on the reaction conditions.

Since reaction via pathway B is followed only by those amines that exhibit some form of steric hindrance,[4,5] it was suggested[3] that this crossover in reaction selectivity at $n = 4$ is also caused by steric hindrance and that it is imparted by the segment $H_2N(CH_2)_4$–. It was postulated[3] that it does so by forming in solution a six-membered coil similar to that described by Newman[6] in his "Rule of Six" to explain the marked decrease in reactivity exhibited by carbonyl compounds that can close a six-membered ring by intramolecular association.

It was shown[7] that a similar pseudoheterocyclic secondary amine configuration can indeed exhibit steric hindrance in the reaction with acetylanthranil, if the integrity of this configuration is maintained by intramolecular hydrogen bonding. Thus, amines such as ethanolamine and anthranilic acid, which associate by intramolecular hydrogen bonding in nonpolar solvents, react with acetylanthranil in benzene via pathway B, but in pyridine or in acetic acid they react via pathway A, owing to intermolecular association of the β-substituted amines with the solvent, which precludes the formation of the cyclic configuration and hence precludes the steric hindrance.[7]

Scheme I



The question now is whether or not the weak force of intramolecular association of the van der Waals type is also sufficient to ensure the integrity of the pseudocyclic configuration in benzene solution. In such a coiled configuration, the $H_2N(CH_2)_4$– segment like the above resembles geometrically, but not electronically, heterocyclic secondary amines, which are known to react with 1 via pathway B owing to steric hindrance.

It was postulated[3] that this small force is sufficient to restrict in aqueous solution the free rotation of the tetramethylene segment about the amino group to which it is attached and therefore to influence disproportionately the steric requirement for hydration of the free amine form, relative to that of the ammonium ion form to account for the entropy effect suggested by Brown.[2c] In contrast to the chemical aberration noted in aqueous solution, the affinity of the amines $H_2N(CH_2)_nH$ for a proton in the gas phase is quite normal as pointed out by Aue.[8] This observation is not unexpected or inconsistent, since these molecules in the gas phase are in a higher energy state, which is sufficient to overcome the weak force of intramolecular association that supports the coiled configuration in aqueous solution. Consequently the methylene chain in the gas phase should remain in a more open or extended configuration, which does not interfere with the approach of a proton or enhance dissociation of the ammonium ion as is assumed to be the case in aqueous solution.

If this postulation is correct, then the sets of amines $H_2N(CH_2)_nZ$, where the ω group Z is a polar group, such as OH (**2b**) or CO_2H (**2c**), should not exhibit the chemical aberration that is exhibited in solution at room temperature by the set **2a**, where Z = H. The relatively strong force of intermolecular hydrogen bonding with the sets **2b** and **2c** should easily overcome the weaker force of intramolecular van der Waal's association extant in the set **2a** to ensure that the amines **2b** and **2c** remain in open configuration, especially in a polar solvent, as shown in Scheme II. Accordingly, long-chain aliphatic amines with a polar substituent in the ω positions should behave chemically toward electrophilic reagents like simple short-chain aliphatic amines such as ethylamine.

Support for this premise can be found in the data published by Girault and Rumpt, who reported[9] in 1958 that unlike the amines $H_2N(CH_2)_nH$ the pK_a values for the amines $H_2N(CH_2)_nOH$ (**2b**) ($n = 0$ to 6) increase monotonically from 5.96 for $n = 0$ to 10.62 for $n = 6$. On the basis of these data, however, one cannot say unequivocally that the chemical

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Table I. Products Isolated from the Reaction of 1 with $H_2N(CH_2)_nZ$, 2

Amine Series	Reaction conditions: n	Z	Solvent	Temp, °C	Time	% units of 1 isolated as: 4	3	5	Calcd selectivity A/B = (3 and/or 5)/4
2a	<4	H	Benzene	rt	4 h	0	*a*	*a*	>16/1[a]
	≥4	H	Benzene	rt	1 day	*a*	0	0	>1/23[a]
2b	2	OH	Neat	rt	1 day	*b*	0	0	>1/25[b]
	2	OH	Pyridine	rt	1 day	0	0	*b*	<50/1[b]
	3	OH	*c*	80	20 min	*b*	0	*b*	2/1[b]
	3	OH	Pyridine	rt	1 day	*b*	0	*b*	17/1[b]
	3	OH	Neat	rt	1 day	0	0	*b*	>50/1[b]
	6	OH	*c*	100	1 h	0	0	62	>50/1[d]
2c	2	CO_2H	Acetic acid	Reflux	3 h	0	0	100	>50/1
			Pyridine	rt	1 day	0	0	95	>50/1
	3	CO_2H	Acetic acid	rt	1 wk	0	0	80	>50/1[e]
			Pyridine	rt	1 day	0	0	100	>50/1
	5	CO_2H	Acetic acid	rt	1 wk	0	0	80	>5/1[f]
			Pyridine	rt	1 day	0	0	100	>50/1
2d	6	*g*	*c*	100	4 h	90	0	0	<1/25

[a] Data taken from ref 3. [b] Data taken from ref 7. [c] 1 made to react with an equivalent weight of amine by fusion at the temperature indicated. [d] 17% of the units of 1 isolated as 6-(*o*-acetamidobenzcarboxy)-*n*-hexylamine, **2d**, and 16% isolated as **4d**, the *o*-acetamidobenzamide of **2d**. [e] 14% of the units of 1 were isolated as *o*-acetamidobenzoic acid. [f] 20% of the units of 1 were isolated as *o*-acetamidobenzoic acid, indicative that these reactions (notes e and f) were not yet complete when terminated. [g] The group is *o*-$(CH_3CONH)PhCO_2$.

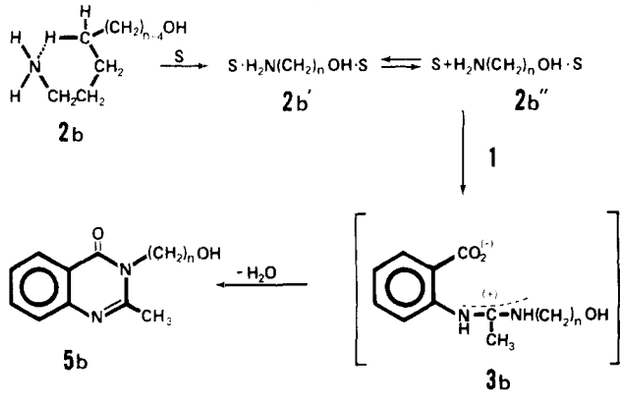
Table II. Characterization Data for Reaction Products 4 and 5 in Table I

Product	Registry no.	mp, °C	Key IR[a] abs bands in μm	NMR[b] data in τ values
Amide				
4d (*n* = 6) from amine **2d** (*n* = 6)	65453-00-1 65453-01-2	144–5	3.0, 3.1, 5.8, 6.0, 6.2, 6.3, 6.6	($CDCl_3$) 1.2–3.0 (cpx, Ar, −1.2 and 3.5 (br, NH), 5.63 (t, CH_2O), 6.52 (q, CH_2NH), 7.75 and 7.80 (s, CH_3), 8.0–8.6 $(CH_2)_4$
Quinazolones				
5b (*n* = 6) from amine **2b** (*n* = 6)	65452-92-8 4048-33-3	120–1	2.9, 6.1, 6.3	($CDCl_3$) 1.6–2.7 (cpx, Ar), 5.88 (t, CH_2N), 6.32 (t, CH_2O), 7.34 (s, CH_3), 7.63 (s, OH), 8.0–8.6 $(CH_2)_4$
5c (*n* = 2) from amine **2c** (*n* = 2)	65452-93-9 107-95-9	218–20	3.3–4.3, 5.9, 6.3, 6.4	
5c (*n* = 3)	65452-94-0	114–5 141–2[d]	3.0–4.3, 5.7, 5.9, 6.1, 6.3, 6.4	(Me_2SO-d_6) 1.7–2.6 (cpx, Ar), 5.88 (t, CH_2N), 7.33 (s, CH_3), 7.57 (t, $CH_2C{=}O$), 8.06 (cpx, CH_2)
5c (*n* = 5)	65453-02-3	179–80	3.2–4.3, 5.8, 6.0, 6.3, 6.4	
Amine				
2d (*n* = 6)[c]		Oil	3.1 br, 5.8, 6.1, 6.3, 6.6	

[a] br = broad. [b] cpx = complex, br = broad, t = triplet, q = quartet, s = singlet. [c] *o*-$(CH_3COHN)PhCO_2(CH_2)_6NH_2$, i.e., the *o*-acetamidobenzoate of amine **2b** (*n* = 6). [d] Hydrates.

aberration in pK_a as a function of *n* noted in the set **2a** was avoided in the set **2b** because steric hindrance to formation of the ammonium ion was avoided or that the reverse reaction was suppressed by avoiding the entropy effects noted by Brown,[2c] or both, since pK_a is only a measure of the equilibrium state of the system.

Scheme II

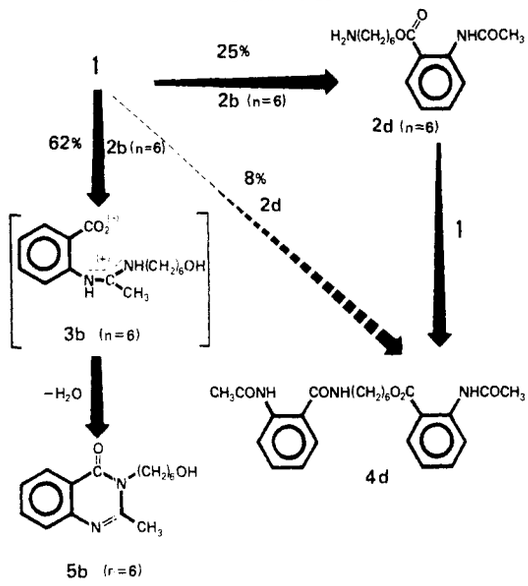


The product distribution obtained in the reaction of amines with acetylanthranil is a more definitive test, since the products are formed irreversibly and therefore the reaction selectivity will indicate the presence or absence of steric hindrance to the forward reaction only. Accordingly, acetylanthranil was made to react with the amino alcohols $H_2N(CH_2)_nOH$ (**2b**) (*n* = 2, 3, and 6). These results are collected in Table I for easy comparison with results obtained earlier[3] with the amines $H_2N(CH_2)_nH$ (**2a**). The corresponding characterization data for the products of reaction with **2b** are collected in Table II.

In contrast to the results obtained with **2a**, the data show that the amino alcohols **2b** follow pathway A preferentially for the values of *n* > 2 and even for *n* = 2 when the reaction is carried out in a polar solvent as mentioned earlier.

To make certain that this remote control on reaction selectivity of the amino group in the ω position is not unique to ω-substituted amino alcohols, acetylanthranil was made to

Scheme III



react with the carboxylic acids $H_2N(CH_2)_nCO_2H$ (**2c**) (n = 2, 3, and 5). Again the reaction products were separated and identified and the selectivity was calculated from the product distribution as described previously.[9] These data are also collected in Table I and the characterization data for the products isolated are collected in Table II. As expected, the selectivity data show that all the amines in the set **2c** follow pathway A preferentially. This uniform result is in sharp contrast to that obtained with the set **2a**, which shows crossover in selectivity from pathway A to B at n = 4.

That this remote control over reaction selectivity is attributable to intermolecular hydrogen bonding by the polar groups at the terminal positions is demonstrated further by the results obtained with 6-(2-acetamidobenzcarboxy)-n-hexylamine (**2d**) (n = 6), which was isolated as a component of the complicated product mixture obtained when 6-amino-n-hexanol-1 (**2b**) (n = 6) was made to react with an equivalent amount of acetylanthranil by fusion at 100 °C. In this reaction 62% of the acetylanthranil units was isolated as N-(6-hydroxyhexamethylene)-2-methylquinazol-4-one (**5b**) (n = 6), 17% as 6-(2-acetamidobenzcarboxy)-n-hexylamine (**2d**) (n = 6), and 16% as **4d**, the o-acetamidobenzamide of **2d**. The formation of these products can be rationalized as outlined in Scheme III. That **4d** (n = 6) was indeed formed from **2d** (n = 6) was demonstrated when **2d** (n = 6) was made to react with an equivalent amount of **1** by fusion at 100 °C to give **4d** (n = 6) as the major product of reaction, exclusive of the alternative possible product [i.e., the 2-acetamidobenzoate ester of **5b** (n = 6)]. This result indicates that selectivity reverts to pathway B, inferring steric hindrance, when the possibility for intermolecular hydrogen bonding is decreased owing to esterification of the terminal OH group.

The results obtained in this investigation are consistent with the hypothesis that the amines $H_2N(CH_2)_4(CH_2)_{n-4}Z$ exhibit steric hindrance to reaction with electrophiles when Z is H owing to the $H_2N(CH_2)_4$– segment, which assumes a six-membered Newman coil configuration. When Z is a polar substituent, however, the intramolecular force that holds the cyclic configuration is overcome by intermolecular hydrogen bonding so that the amine can now react with the electrophilic reagent without steric hindrance.

Experimental Procedures

The general procedure for reaction of acetylanthranil (**1**) with aliphatic amines **2** and the separation and identification of the products **3**, **4**, and **5** are described in preceding publications.[3,5,7] The materials balance of products with reactants was usually more than 90% so that reliable calculation of the reaction selectivity could be made from the corresponding product distribution as noted in Table I. Characterization data for the products isolated are collected in Table II. Specific details and slight modifications in procedure to accommodate the bifunctional amines investigated are noted below.

A. Reaction of 1 with the Amines $H_2N(CH_2)_nH$ (2a) in Benzene. These procedures are described in ref 3.

B. Reaction of 1 with the Amines $H_2N(CH_2)_nOH$ (2b). (i) ethanolamine **2b** (n = 2) is described in ref 7; (ii) 3-amino propanol (**2b**) (n = 3) is described in ref 7; (iii) 6-amino-n-hexanol-1 (**2b**) (n = 6).

Acetylanthranil (5 g) and 6-amino-n-hexanol-1 (**2b**; n = 6) (5 g) were warmed on a steam bath for 1 h. The solution was allowed to cool to room temperature overnight. The solid product was ground to a fine powder and then leached sequentially with cold dilute aqueous base and aqueous acid. The IR and NMR spectra of the insoluble residue (1.1 g) indicated that this material was **4d** (n = 6), i.e., the 2-acetamidobenzamide derivative of 6-(2-acetamidobenzcarboxy)-n-hexylamine (**2d**) (n = 6). Recrystallization of this amido ester from methanol gave **4d** (n = 6) in the form of colorless crystals (mp 144–145 °C). The assigned structure of the recrystallized product was verified by its NMR and IR spectra (Table II). The aqueous acid extract was made alkaline with dilute aqueous base and a viscous orange oil (1.6 g) separated from solution. The IR spectrum (Table II) of this oil indicated that this product was 6-(2-acetamidobenzcarboxy)-n-hexylamine (**2d**) (n = 6). A sample of the oil (1 g) was fused with an equal weight of acetylanthranil to give **4d** (n = 6) in good yield (1.5 g; mp 142–144 °C) (no depression with the above sample). The aqueous alkaline mother liquor from which **2d** (n = 6) was separated was allowed to remain at room temperature overnight, during which time N-(6-hydroxy-n-hexyl)2-methylquinazol-4-one (**5b**) (n = 6) separated in the form of a white powder (4.8 g; mp 120–121 °C). The assigned structure was confirmed by its IR and NMR spectra (Table II). Thus 62% of the acetylanthranil units were isolated as **5b** (n = 6), 17% as **2d** (n = 6), and 16% as **4d** (n = 6).

C. Reactions with the Amines $H_2N(CH_2)_nCO_2H$, (2c). i. 3-Aminopropionic Acid (n = 2). A solution of **1** (5 g) and 3-aminopropionic acid (**2c**) (n = 2) (5 g) in acetic acid (60 cm^3) was allowed to react at reflux for 3 h. The solution was cooled to room temperature and then added to 500 cm^3 of cold water to cause precipitation of the product as a white powder (8 g), which was soluble in $NaHCO_3$. Recrystallization from hot water gave the product in the form of white crystals (7.2 g; mp 218–220 °C) which were identified as N-(2-carboxyethyl)-2-methylquinazol-4-one (**5c**) (n = 2) by its IR spectrum (Table II) and by its elementary analysis. Anal. Calcd for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.49; NE, 232.2. Found: C, 62.1; H, 5.3; N, 12.1; NE, 228.

The quinazolone carboxylic acid was also obtained in good yield when the reaction was repeated using pyridine as solvent at room temperature. The reaction mixture was separated essentially as described in detail for reaction of **1** with **2c** (n = 5).

ii. 4-Aminobutyric Acid (n = 3). A solution of **1** (5 g) and 4-aminobutyric acid (**2c**) (n = 3) (5 g) in acetic acid (50 cm^3) was allowed to react at room temperature for 1 week. The excess solvent was removed at about 10 mmHg pressure in a rotary film evaporator. The nonvolatile product was leached with water to dissolve the acetamidine salt, leaving a powdery residue (0.8 g; mp 182–183 °C), which was indentified as o-acetamidobenzoic acid by its IR spectrum and mixture melting point with an authentic sample. The mother liquor was allowed to remain at room temperature overnight. During this time the acetamidine salt was converted to the corresponding quinazolone carboxylic acid, which precipitated from solution as a white powder. The powder was recrystallized from hot water to give the product in the form of white crystals (6.5 g), which melted at 114–115 °C with evolution of a gas, solidifed, and remelted at 141–142 °C. A sample was fused at 120 °C until bubbling was completed to give a white solid that remelted at 140 °C. The IR and NMR spectra, Table II, indicated that the sample melting at 114 °C and that at 141 °C were hydrates of N-(3-carboxypropyl)-2-methylquinazol-4-one (**5c**) (n = 3).

Thus 14% of the acetylanthranil units were recovered as acetylanthranilic acid, indicating incomplete reaction, and 80% were recovered as the quinazolone carboxylic acid **5c** (n = 3).

Conversion of **1** to the quinazolone carboxylic acid was 90% complete when the reaction was allowed to occur overnight in pyridine at room temperature. The product was isolated essentially as described in detail for reaction of **1** with **2c** (n = 5).

iii. 6-Aminocaproic Acid (n = 5). A solution of **1** (5 g) and 6-aminocaproic acid (**2c**) (n = 5) (4.0 g) in acetic acid (30 cm^3) was al-

lowed to react at room temperature for 1 week; the reaction mixture was separated essentially as described in detail for reaction of 1 with **2c** (n = 3). About 20% of the acetylanthranil units were recovered as o-acetamidobenzoic acid (mp 185–186 °C) and the rest was isolated as N-(5-carboxy-n-pentyl)-2-methylquinazol-4-one (**5c**) (n = 5) (mp 179–180 °C). The assigned structure was verified by its IR spectrum and by its NE (calcd 274; obsd 277).

Another solution of 1 (5 g) and **2c** (n = 5) in pyridine (40 cm^3) was allowed to react at room temperature overnight. During this time the quinazolone product separated as a white powder (4.8 g; mp 169–171 °C), which was removed by filtration. The mother liquor was evaporated to dryness at 60 °C (10 mmHg). The nonvolatile semisolid residue was leached with water to remove pyridine. The IR spectrum of the crystalline residue (3.1 g; mp 172–175 °C) was essentially the same as that fraction melting at 169–171 °C (no depression in melting point with a mixed sample). The two fractions were combined and recrystallized from hot water to give N-(5-carboxy-n-pentyl)-2-methylquinazol-4-one (**5c**) (n = 5) in the form of white crystals (7.3 g; 179–180 °C). The IR spectrum of this sample was identical to that obtained via reaction in acetic acid.

Registry No.—**1**, 525-76-8; **2c** (n = 3), 56-12-2; **2c** (n = 5), 60-32-2; o-acetamidobenzoic acid, 89-52-1.

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Acylanthranils. 8. Question of Newman Steric Hindrance in the Reaction of Linear Aliphatic Amines with Acetylanthranil[1]

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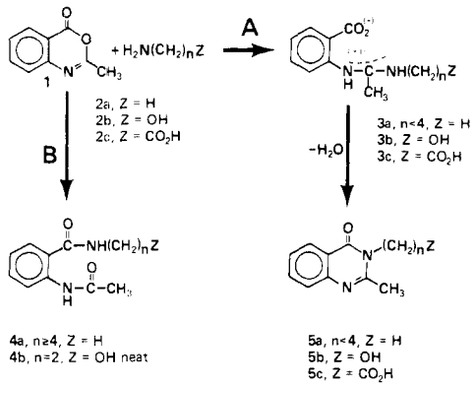
Although hydrocarbon amines with the general formula $H_2N(CH_2)_4R$ (**2**) react "abnormally" with acetylanthranil (**1**) to give the corresponding o-acetamidobenzamide (**4**), analogous amines that do not have a hydrogen atom at the critical fourth carbon position removed from the amino group react "normally" with **1** to give the corresponding acetamidine salt **3**. These results support the premise that the "abnormal" selectivity is caused by the aminotetramethylene segment, which forms a six-membered Newman coil due to intramolecular van der Waals attraction of hydrogen for nitrogen.

It was reported[2,3] that the reaction selectivity of acetylanthranil with the linear aliphatic amines $H_2N(CH_2)_nH$ is dependent upon the number of methylene groups in the aliphatic chain. When $n < 3$ the reaction follows pathway A exclusively to give the corresponding acetamidine intermediate **3** or its cyclodehydration product **5**, but when $n > 3$ the reaction follows pathway B exclusively to give the corresponding o-acetamidobenzamide (**4**) as shown in Scheme I. Reaction with n-propylamine (**2a**) (n = 3) follows both pathways in the relative ratio of A/B > 17/1.

Since pathway B is associated with amines that exhibit steric hindrance to reaction with other electrophiles, whereas pathway A is associated with amines that do not,[4] it was suggested[3] that steric hindrance is also responsible for the sharp crossover in reaction selectivity with **1** at n = 4, and it was postulated further that this steric hindrance is caused by the $H_2N(CH_2)_4$– segment, which is held in the form of a six-membered ring by the small force of intramolecular association of the van der Waals type[3] as shown in Figure 1. Such a configuration is similar to that proposed by Newman[5] in his "Rule of Six" to explain the observed marked decrease in rate of saponification for amides and esters of aliphatic acids with more than three carbon atoms in the chain.

Scheme I



Support of this point of view is found in the observation[6] that the long-chain aliphatic amines $H_2N(CH_2)_nOH$ (**2b**) and $H_2N(CH_2)_nCO_2H$ (**2c**) react with **1** via pathway A, showing that interaction with **1** occurs without steric hindrance, when the long-chain amine has a polar group in the ω position. This remote control by the polar substituent, OH or CO_2H, on the reaction selectivity of the NH_2 group at the other extremity is attributed to the intermolecular hydrogen bonding, especially in a polar solvent, which serves to overcome the weak force of intramolecular van der Waals association that supports the Newman coil. Thus, the ω-substituted amine is kept in a more open configuration, which enables interaction to occur with **1** via pathway A as described previously.[6] Analogous results were obtained[7] with anthranilic acid (**2d**) and with ethanolamine (**2b**) (n = 2). In nonpolar solvents, or neat, these amines interacted with **1** via pathway B, owing to intramolecular hydrogen bonding that formed six- and five-membered rings, respectively. In polar solvents, such as pyridine or acetic acid, however, these amines interacted with **1** via pathway A, since the ring structure that imparted steric hindrance in the

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